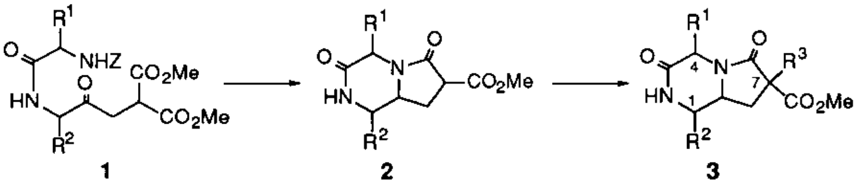
STUDIES ON THE SYNTHESIS OF SUBSTITUTED 3,6-DIOXOPERHYDROPYRROLO[1,2-*a*]PYRAZINES AS NON-PEPTIDE SCAFFOLDS FOR PEPTIDOMIMETICS

Mercedes Martín-Martínez, Mª Teresa García-López, Rosario Herranz, and Rosario González-Muñiz*

Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain

Abstract– Intramolecular reductive amination of 4-keto diesters, derived from Z-Xaa-Yaa dipeptides, and subsequent γ-lactamization is a versatile method for the preparation of 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines bearing amino acid side chains at C-1, C-4 and C-7 positions, as Xaa-Yaa-Zaa (Yaa ≠ Gly) tripeptide mimetics.

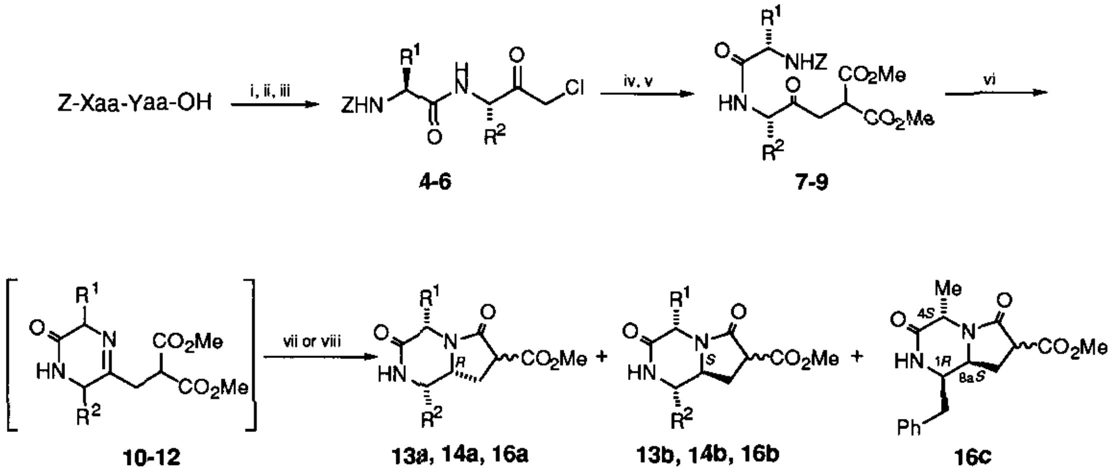
The development of small organic molecules as non-peptide scaffolds carrying the pharmacophore amino acid side chains in a conformation that mimic their orientation on the bioactive peptide is a current approach to the search of peptidomimetics.[1-4] Among the variety of heterocyclic templates which have been successfully applied to this search, lactams have proved to be privileged structures.[5-7] Based on these considerations, and on the well known proposal of Ariëns and Farmer[8] about the possibility to obtain high receptor binding affinity with three appropriately oriented pharmacophores, we focused our attention on the 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine system, as template that could theoretically carry amino acid side chains in positions 1, 4, and 7. Our first goal was to devise a synthetic route for the construction of the nitrogen bridged bis-lactam, which would allow the incorporation of substituents into such positions, from easily available compounds. To this purpose, we planned the route indicated in Scheme 1 involving the intramolecular reductive amination of the 4-keto diesters (**1**), derived from suitable protected dipeptides, and subsequent γ-lactamization as key steps. Following this route, we recently described the preparation of 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines (**3**) (R^2=H) as Xaa-Gly-Yaa mimetics from Z-Xaa-Gly-OH.[9] Our next goal was to know whether this synthetic approach is versatile enough to give access to compounds (**3**) with an appended amino acid side chain at C-1 (R^2≠H). To this aim, we have studied the extension of this route to the synthesis of Xaa-Yaa-Zaa (Yaa≠ Gly) mimetics from Z-Xaa-Yaa-OH dipeptides.



Scheme 1

RESULTS AND DISCUSSION

The starting 4-keto diesters (**7-9**) were synthesized by alkylation of dimethyl malonate with the halomethyl ketones (**4-6**), which were prepared from the corresponding Z-Xaa-Yaa-OH dipeptides following a similar procedure to that previously reported for other dipeptide derivatives (Scheme 2).[9]



i) iBuOCOCl/ NMM, ii) CH_2N_2, iii) HCl/ MeOH, iv) NaI, v)NaCH(CO_2Me), v i)H_2/10% Pd-C/ MeOH, v ii)$NaBH_3CN$/ MeOH

Compd	R^1	R^2	Xaa	Yaa
4, 7, 10, 13	H	Me	Gly	Ala
5, 8, 11, 14	H	CH_2Ph	Gly	Phe
6, 9, 12, 16	Me	CH_2Ph	Ala	Phe

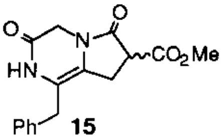
Scheme 2

Catalytic hydrogenation of the Z-Gly-Ala-OH derived 4-keto diester (**7**) provided the corresponding perhydropyrrolopyrazines (**13a**) and (**13b**) (**a**/**b**: 3:1) in good yield (Scheme 2, Table 1). However, a similar reaction of the Phe derivative (**8**) afforded the desired bicyclic lactams (**14a**) (15%) and (**14b**) (5%) in low yield, while the partially unsaturated $\Delta^{1,8a}$-hexahydropyrrolopyrazine (**15**) was obtained as the major product. The formation of compound (**15**) can be easily explained by generation of the imine intermediate (**11**), imine-enamine tautomerism and subsequent γ-lactamization. In fact, imine (**11**) was isolated when the catalytic hydrogenation was stopped after disappearance of the starting 4-keto diester.

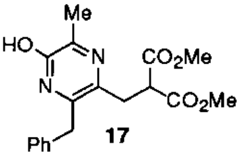
Concerning the stereochemical course of the catalytic hydrogenation involved in the construction of the pyrrolo[1,2-*a*]pyrazine skeleton in **13** and **14**, it can be noted that it proceeds stereoselectively to provide the 8a*R* diastereoisomers as the major compounds (Table 1). This result can be rationalized by the hydrogenation of the imine intermediates in such a way that the hydrogen enters by the opposite side to the R^2 substituent. The absolute configuration at C_{8a} was assigned by means of the $J_{1,2}$ and $J_{1,8a}$ coupling constant values. Thus, $J_{1,2}$ values of 0 Hz for the bicyclic lactams (**13b**) and (**14b**) indicated an H_1-C_1-

N_2-H_2 torsional angle of approximately 90° and, therefore, an axial disposition of the H_1 hydrogen. However, values of $J_{1,2}$ between 1.5 and 4.9 Hz, as for derivatives (**13a**) and (**14a**), are in agreement with an equatorial disposition of this hydrogen. Finally, the $J_{1,8a}$ coupling constant values in the ^1H NMR spectra of compounds (**13a**) and (**14a**) ($J_{1,8a}$=3.4-4.0 Hz) allowed us to assign the *R* configuration at C_{8a} for these compounds and the *S* configuration for **13b** and **14b** ($J_{1,8a}$ ~9.5 Hz).

We previously reported that, in the case of the 1-unsubstituted 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine analogues, the reduction of the corresponding imine intermediates with $NaBH_3CN$ gave better yields and higher diastereomeric excesses than those obtained by using catalytic hydrogenation.[9] Then, $NaBH_3CN$ was employed for the reductive amination of the keto diester (**8**). As shown in Table 1, the yield of **14** was significantly improved but no stereoselectivity was found. A similar reaction starting from the keto diester (**9**) provided a mixture of compounds (**16a**) (36%), (**16b**) (20%) and (**16c**) (4%). In the case of derivative (**16c**) it was possible to separate the two epimers at C-7 by chromatography. Traces of (1*R*,4*S*,7*R*,*S*,8a*R*) diastereomes (≈2%) were also detected in the ^1H NMR spectrum of the crude reaction products. Attempts to use the catalytic hydrogenation reaction to the synthesis of 1,4-disubstituted pyrrolo[1,2-*a*]pyrazines from Z-Ala-Phe derived 4-keto diester (**9**) led to complex reaction mixtures from which only the 2-hydroxypyrazine (**17**) was isolated.[10] This result seems to indicate that the imine intermediate (**12**), that was isolated and characterized after disappearance of the starting keto diester, cannot be reduced under the used hydrogenation conditions, but evolves to different compounds, including the aromatic derivative (**17**), probably *via* a imine-enamine tautomerism, and dehydrogenation with palladium on carbon.



15



17

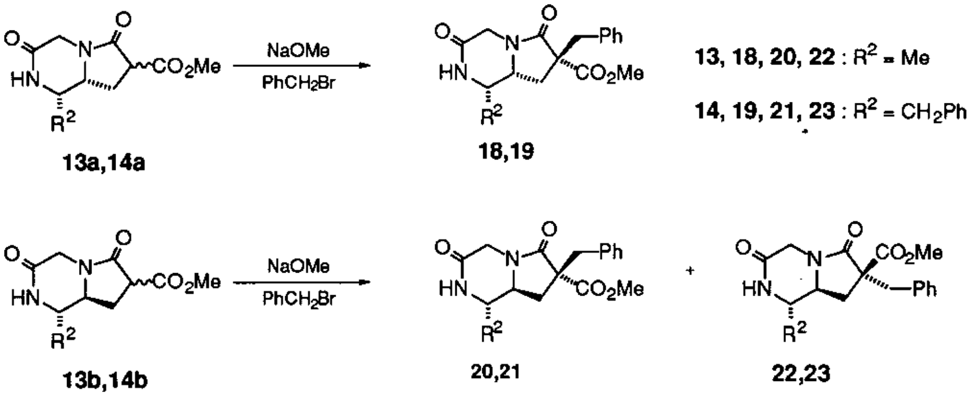
Table 1. Results of the Preparation of 3,6-Dioxoperhydropyrrolo[1,2-*a*]pyrazines from 4-Keto Diesters Derived from Z-Xaa-Yaa-OH

Dipeptide	4-Ketodiester	Reduction method	Reaction time(days)	Final Compds.	Yield[a] (%)	a/b ratio[b]	Others (Yield, %)
Z-Gly-Ala-OH	**7**	H_2/Pd-C	2	**13a+13b**	70	3:1	–
Z-Gly-Phe-OH	**8**	H_2/Pd-C	5	**14a+14b**	20	3:1	**15** (32)
Z-Gly-Phe-OH	**8**	$NaBH_3CN$	1	**14a+14b**	54	1:1	–
Z-Ala-Phe-OH	**9**	$NaBH_3CN$	1	**16a+16b**	56	1.8:1	**16c** (4)
Z-Ala-Phe-OH	**9**	H_2/Pd-C	5				**17** (11)

[a] Yield of isolated perhydropyrrolo[1,2-*a*]pyrazines. [b] Measured by HPLC from the crude reaction mixtures.

The absolute configurations at C_1, C_7 and C_{8a} in **16a**, **16b** and **16c** were assigned by means of the coupling constants values and NOE experiments. As previously indicated for compounds (**13**) and (**14**), the $J_{1,8a}$ value of approximately 3 Hz for **16a** indicated a *cis* relationship between H_1 and H_{8a} hydrogens, while $J_{1,8a}$ values of ~10 Hz in **16b** agreed with a *trans* disposition of these hydrogens. Concerning NOE experiments, isomers (**16a**) show a weak NOE between the protons of 1-CH_2 and 4-CH_3 groups indicating that these substituents are located in the same face of the heterocyclic ring. On the other hand, diastereomers (**16b**) show a NOE between the respective H_{8a} proton and the 4-CH_3 group and, therefore, the configuration at C_{8a} for these isomers was assigned as *S*. Diastereomers (**16c**) showed $J_{1,2}$ and $J_{1,8a}$ values of 0 and 3 Hz respectively, and a marked shielding of the H_1, H_4 and H_{8a} protons, consistent with a *cis* fusion of the bicyclic ring.[11] Moreover, these compounds show a weak NOE between H_{8a} protons and the protons of the 4-CH_3 group. All these data are in agreement with 1*R*,4*S*,8a*S* or 1*S*,4*R*,8a*R* configuration in which the bicyclic ring adopts *cis* conformation in order to avoid the axial disposition of substituents at positions 1 and 4, as it would be in a *trans*-fused conformation. The isolation of enamine derivatives, such as **15**, and the described racemization in other related bicyclic systems, such as the 8-amino-3-oxoindolizines,[12] support that, in this case, the epimerization takes place at C_1 position. This epimerization could be due to an imine-enamine equilibrium favoured by the presence of substituents in position α to the imine carbon. The percentage of epimerization at C_1 was calculated to be 11%.

Finally, with compounds (**2**) ($R^2 \neq$ H) in hand, we decided to verify the possibility of replacing the *C*-terminal Gly residue in this Xaa-Yaa-Gly mimetics with other amino acid side chains. To this aim, we studied the incorporation of the Phe side chain into position 7 of perhydropyrrolo[1,2-*a*]pyrazine derivatives with different configuration at C-8a as representative examples (Scheme 3).



Scheme 3

The alkylation of the 8a*R* derivatives (**13a**) and (**14a**) gave almost exclusively the 7*R*-benzyl derivatives (**18**) and (**19**), respectively, while alkylation of the 8a*S* analogues (**13b**) and (**14b**) led to a mixture of the two possible C_7 epimers (**20** + **22**) and (**21** + **23**), in which the 7*S*,8a*S* diastereomer was predominant in both cases (Table 2). These results support a preferential attack of the alkyl halide from the opposite side to the unshared lone pair on the lactam nitrogen.[9,13] The differences in the stereoselectivity found for the 8a*R* and 8a*S* diastereomers could be explained in terms of the axial and equatorial disposition, respectively, of the substituent in position 1. The absolute configuration at C-7 of all the 7-benzyl derivatives was established by comparison of their H_{8a} chemical shifts with those of the H_{8a} protons in the corresponding nonbenzylated analogues, as previously reported for related compounds.[9]

Table 2. Results of the Alkylation of Compounds (**13**) and (**14**) with Benzyl Bromide.

Starting Compd	Final Compd	Yield (%)	7*R*,8a*R*/7*S*,8a*R* Ratio[a]	7*R*,8a*S*/7*S*,8a*S* Ratio[a]
13a	**18**	57	1:0[b]	-
13b	**20+22**	56	-	1:3.5
14a	**19**	52	1:0[b]	
14b	**21+23**	34		1:3

[a] Estimated by ^{1}H NMR. [b] Traces of (7*S*,8a*R*) diastereomers were detected in the ^{1}H NMR spectra.

In summary we have now demonstrated that the reductive amination of 4-keto diesters derived from dipeptides is a flexible method for the preparation of the 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine scaffold with some amino acid side chains at C-1, C-4 and C-7 positions in different spatial arrangements. The use of $NaBH_3CN$ as reducing agent shortens the reaction time, improves the total yield and confers more generality to the method, specially in the case of derivatives substituted at the C-1 position.

EXPERIMENTAL PROCEDURES

^{1}H NMR spectra were recorded with a Varian EM 390, a Varian Gemini 200 or a Varian XL-300 spectrometer operating at 90, 200 or 300 MHz, respectively, using TMS as internal standard. ^{13}C NMR spectra were registered on a Varian Gemini 200 (50 MHz). UV absorption spectra were taken with a Perkin-Elmer 550 SE spectrophotometer using EtOH as sample solvent. Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were obtained on a CHN-O-RAPID instrument. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F254 (Merck). Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Z-protected dipeptides were purchased from Bachem

Synthesis of chloromethyl ketones derived from Z-Xaa-Yaa-OH dipeptides

General Procedure. To a solution of the Z-Xaa-Gly-OH dipeptide (18 mmol) in dry THF (40 mL) were successively added, at -20°C, *N*-methylmorpholine (2.3 mL, 21 mmol) and isobutyl chloroformate (2.7 mL, 21 mmol). After stirring for 15 min at -20°C, an ethereal solution of diazomethane (from *N*-nitroso-*N*-methylurea, 6 g) was added. After 30 min of reaction, a solution of 2N HCl/MeOH (15 mL, 30 mmol) was added and the stirring continued until N_2 evolution ceased. The solution was neutralized with Et_3N and the solvents were evaporated. The resulting residue was dissolved in EtOAc (150 mL), washed with H_2O and the organic layer was dried over Na_2SO_4. Evaporation and precipitation from Et_2O or purification on a silica gel column, using the solvent system specified in each case, afforded the following compounds:

Z-Gly-Ala-CH_2-Cl (4). Yield 68%, foam. Chromatographic solvent system: EtOAc/Hexane (1:1). ^1H NMR (90 MHz, $CDCl_3$): δ 1.4 (d, J= 6.0 Hz, 3H, β-CH_3 Ala), 3.9 (m, 2H, α-CH_2 Gly), 4.2 (s, 2H, CH_2Cl), 4.8 (t, J= 6.0 Hz, 1H, α-CH Ala), 5.1 (s, 2H, CH_2 Z), 5.7 (m, 1H, α-NH Gly), 6.9 (d, J= 7.5 Hz, 1H, α-NH Ala), 7.2-7.3 (m, 5H, C_6H_5 Z). Anal. Calcd for $C_{14}H_{17}N_2O_4Cl$: C 53.57, H 5.48, N 8.96, Cl 11.34. Found: C 53.51, H 5.69, N 9.03, Cl 11.09.

Z-Gly-Phe-CH_2-Cl (5). Yield 67%. Precipitated with Et_2O. White solid, mp 95-97°C (Et_2O). ^1H NMR (90 MHz, $CDCl_3$): δ 3.1 (m, 2H, β-CH_2 Phe), 3.6 (m, 2H, α-CH_2 Gly), 3.9 (s, 2H, CH_2Cl), 4.9 (m, 3H, α-CH Phe, CH_2 Z), 5.4 (m, 1H, α-NH Gly), 6.7 (d, J= 7.2 Hz, 1H, α-NH Phe), 6.9-7.2 (m, 10H, C_6H_5 Ph, Z). Anal. Calcd for $C_{20}H_{21}N_2O_4Cl$: C 61.78, H 5.44, N 7.20, Cl 9.12. Found: C 61.58, H 5.53, N 7.05, Cl 9.14.

Z-Ala-Phe-CH_2-Cl (6). Yield 51%. Precipitated with Et_2O. White solid, mp 128-130°C (Et_2O). ^1H NMR (90 MHz, $CDCl_3$): δ 1.2 (d, J= 7.8 Hz, 3H, β-CH_3 Ala), 3.0 (m, 2H, β-CH_2 Phe), 4.0 (s, 2H, CH_2Cl), 4.2 (m, 1H, α-CH Ala), 4.8 (m, 1H, α-CH Phe), 5.0 (s, 2H, CH_2 Z), 5.2 (d, J= 8.2 Hz, 1H, α-NH Ala), 6.8 (d, J= 7.8 Hz, 1H, α-NH Phe), 7.0-7.3 (m, 10H, C_6H_5 Ph, Z). Anal. Calcd for $C_{21}H_{23}N_2O_4Cl$: C 62.61, H 5.75, N 6.95, Cl 8.80,. Found: C 62.67, H 5.67, N 6.91, Cl 8.55.

Synthesis of 4-keto diesters derived from Z-Xaa-Yaa-OH dipeptides.

General Procedure. A mixture of the corresponding chloromethyl ketone (9 mmol) and sodium iodide (1.35 g, 9 mmol) in THF (30 mL) was stirred at rt for 10 min and then added to a solution of freshly prepared mono sodium salt of dimethyl malonate (1.54 g, 10 mmol) in THF (20 mL). Stirring was continued for 3-15 h, the solvent was removed and the residue was extracted with EtOAc (100 mL) and washed with H_2O (75 mL). The organic layer was dried (Na_2SO_4) and evaporated leaving a residue which was purified on a silica gel column using a gradient from 25 to 50% of EtOAc in hexane.

Methyl 5(*S*)-[(*N*-benzyloxycarbonyl)glycyl]amino-2-methoxycarbonyl-4-oxohexanoate (7). Yield 59%, foam. ^1H NMR (90 MHz, $CDCl_3$): δ 1.3 (d, J= 6.7, 3H, H–6), 3.0 (dd, J= 7.5 and 3.0 Hz, 2H, H-3), 3.6 (s, 6H, CO_2CH_3), 3.8 (m, 2H, α-CH_2 Gly), 4.0 (m, 1H, H-2), 4.5 (m, 1H, H-5), 5.0 (s, 2H, CH_2 Z), 5.4 (m, 1H, α-NH Gly), 6.8 (d, J= 8.0 Hz, 1H, 5-NH), 7.1-7.3 (m, 5H, C_6H_5 Z). Anal. Calcd for $C_{19}H_{24}N_2O_8$: C 55.88, H 5.92, N 6.86. Found: C 55.61, H 5.75, N 7.01.

Methyl 5(*S*)-[(*N*-benzyloxycarbonyl)glycyl]amino-2-methoxycarbonyl-6-phenyl-4-oxohexanoate (8). Yield 77%, syrup. ^1H NMR (90 MHz, $CDCl_3$): δ 2.8 (m, 4H, H-3, H–6), 3.5 (s, 6H, CO_2CH_3), 3.6 (m, 2H, α-CH_2 Gly), 3.8 (m, 1H, H-2), 4.7 (m, 1H, H-5), 4.9 (s, 2H, CH_2 Z), 5.3 (m, 1H, α-NH Gly), 6.6 (d, J= 6.9 Hz, 1H, 5-NH), 6.9-7.2 (m, 10H, C_6H_5 Ph, Z). Anal. Calcd for $C_{25}H_{28}N_2O_8$: C 61.97, H 5.82, N 5.78. Found: C 62.15, H 6.01, N 5.66.

Methyl 5(*S*)-[(*N*-benzyloxycarbonyl)-L-alanyl]amino-2-methoxycarbonyl-6-phenyl-4-oxohexanoate (9). Yield: 72%, white solid, mp 98-100°C (EtOAc-hexane). ^1H NMR (90 MHz, $CDCl_3$): δ 1.2 (d, J= 7.5 Hz, 3H, CH_3 Ala), 3.0 (m, 4H, 3-H, 6-H), 3.7 (s, 6H, CO_2CH_3), 3.9 (m, 1H, 2-H), 4.1 (q, J= 7.5 Hz, 1H, α-Ala), 4.8 (m, 1H, 5-H), 5.0 (s, 2H, CH_2-Z), 5.1 (m, 1H, 5-H), 6.6 (d, J= 7.8 Hz, 1H, 5-NH), 7.0-7.3 (m, 10H, C_6H_5 Z, Ph). Anal. Calcd for $C_{26}H_{30}N_2O_8$: C 62.64, H 6.06, N 5.62. Found: C 62.35, H 5.94, N 5.36.

Reductive amination of 4-keto diesters derived from dipeptides

Method A. A solution of the corresponding 4-keto diester (5 mmol) in MeOH (100 mL) was hydrogenated at 40ºC and 40 psi of pressure for 2-5 days (Table 1), using 10 % Pd-C (0.4 g) as catalyst. After filtration of the catalyst, the solvent was evaporated and the resulting residue was purified on a silica gel column as specified.

Method B. A solution of the corresponding 4-keto diester (5 mmol) in MeOH (100 mL) was hydrogenated overnight at rt and 40 psi of pressure in the presence of 10% Pd-C (0.4 g). The catalyst was filtered and $ZnCl_2$ (0.34 g, 2.5 mmol) and $NaBH_3CN$ (0.94 g, 15 mmol) were added to the filtrate. After stirring overnight at rt, the solvent was evaporated to dryness. The residue was extracted with EtOAc (150 mL), and washed successively with 1N HCl, sat. $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4 and, after evaporation of the solvent, the residue was purified as specified.

7-Methoxycarbonyl-1-methyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine (13). Chromatographic solvent system: CH_2Cl_2/MeOH (98:2). Isomers (1*S*, 7*RS*, 8a*R*): **13a**: Yield 52%, foam (From **7**, Method A). Anal. Calcd for $C_{10}H_{14}N_2O_4$: C 53.09, H 6.24, N 12.38. Found: C 52.78, H 6.61, N 12.53. Isomers (1*S*, 7*RS*, 8a*S*): **13b**: Yield 18%, foam (From **7**, Method A). Anal. Calcd for $C_{10}H_{14}N_2O_4$: C 53.09, H 6.24, N 12.38. Found: C 52.91, H 6.37, N 12.43.

1-Benzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine (14). Chromatographic solvent system: Gradient from 1 to 4% of MeOH in CH_2Cl_2. Isomers (1*S*, 7*RS*, 8a*R*): **14a**: Yield 15%, foam (From **8**, Method A) and 27% (From **8**, Method B). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.56, H 6.00, N 9.26. Found: C 63.61, H 6.12, N 9.07. Isomers (1*S*, 7*RS*, 8a*S*): **14b**: Yield 5%, foam (From **8**, Method A) and 27% (From **8**, Method B). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.56, H 6.00, N 9.26. Found: C 63.72, H 5.86, N 9.01.

1-Benzyl-7(*R,S*)-methoxycarbonyl-3,6-dioxo-$\Delta^{1,8a}$-hexahydropyrrolo[1,2-*a*]pyrazine (15). This compound (32%) is obtained from **8** using method A, along with isomers (**14a**) and (**14b**). Slightly yellow solid, mp 180-182°C (EtOAc-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (dd, J=16.1, 10.1 Hz, 1H, H-8), 3.24 (dd, J=16.1, 5.9 Hz, 1H, H-8), 3.45 (m, 2H, H-4), 3.71 (dd, J=10.1, 5.9 Hz, 1H, H-7), 3.83 (s, 3H, CO_2Me), 4.21 (s, 2H, 1-CH_2), 7.15 (s, 1H, H-2), 7.20-7.38 (m 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.63 (C-8), 33.05 (1-CH_2), 44.13 (C-4), 47.31 (C-7), 52.62 (OMe), 110.66 and 114.91 (C-1 y C-8a), 126.59, 128.57, 128.73 and 138.26 (Ph), 162.85, 168.37 and 169.91 (CO). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C 63.99, H 5.37, N 9.33. Found: C 63.71, H 5.49, N 9.12.

1-Benzyl-7-methoxycarbonyl-4-methyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines (16). Chromatographic solvent system: gradient from 17 to 67% of acetone in hexane. Isomers (1*S*, 4*S*, 7*RS*, 8a*R*): **16a**: Yield 36%, foam (from **9**, Method B). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85 Found: C 64.61, H 6.19, N 8.93. Isomers (1*S*, 4*S*, 7*RS*, 8a*S*): **16b**: Yield 20%, syrup (from **9**, Method B). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85 Found: C 64.18, H 6.61, N 8.58. Isomers (1*R*, 4*S*, 7*RS*, 8a*S*): **16c**: Yield 4%, foam (from **9**, Method B). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85 Found: C 64.23, H 6.02, N 8.52.

6-Benzyl-5-[(2,2-dimethoxycarbonyl)ethyl]-2-hydroxy-3-methylpyrazine (17). Chromatographic solvent system: CH_2Cl_2/MeOH (40:1) . Yield 11%, syrup (From **9**, Method A). ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, 3-CH_3), 3.19 (d, J=7.4 Hz, 2H, *CH_2*-CH), 3.74 (s, 6H, CO_2CH_3), 3.96 (s, 2H, 6-CH_2), 4.04 (t, J=7.4 Hz, 1H, CH_2-*CH*), 7.14-7.37 (m, 5H, Ph). UV λ(nm): 328 (8814), 229 (10942). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C 62.78, H 5.85, N 8.13. Found: C 62.70, H 5.71, N 8.24.

Isolation of imine intermediates

Imine intermediates were isolated, after filtration of the catalyst and evaporation of the solvent, when the corresponding hydrogenation reaction was stopped after 4 h.

6(*S*)-Benzyl-5-[2,2-dimethoxycarbonyl)ethyl]-2-oxo-1,2,3,6-tetrahydropyrazine (11). From **8**. ^1H NMR (300 MHz, $CDCl_3$): δ 2.87 (dd, J=13.4, 7.0 Hz, 1H, 6-CH_2), 2.94 (ddd, J=15.8, 7.2, 2.2 Hz, 1H, *CH_2*-CH), 3.10 (ddd, J=15.8, 7.0, 3.6 Hz, 1H, *CH_2*-CH), 3.18 (dd, J=13.4, 4.0 Hz, 1H, 6-CH_2), 3.30 (m, 1H, 3-H), 3.75 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 4.01 (m, 1H, 3-H), 4.03 (t, J=7.0 Hz, 1H, CH_2-*CH*), 4.23 (ddd, J=7.0, 4.0, 2.3 Hz, 1H, 6-H), 6.56 (br s, 1H, 1-H), 7.12-7.35 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.66 (*CH_2*-CH), 40.16 (6-CH_2), 47.82 (CH_2-*CH*), 52.03 (C-3), 52.81 (OMe), 57.70 (C-6), 127.54, 128.92, 129.70 and 134.68 (Ph), 163.82 (C-5), 168.36, 168.60 and 169.55 (CO).

6(*S*)-Benzyl-5-[2,2-dimethoxycarbonyl)ethyl]-3(*S*)-methyl-2-oxo-1,2,3,6-tetrahydropyrazine (12). From **9**. ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, J=7.3 Hz, 3H, 3-CH_3), 2.78 (dd, J=13.9, 8.6 Hz, 1H, 6-CH_2), 2.92 (ddd, J=17.1, 6.9, 1.6 Hz, 1H,*CH_2*-CH), 3.18 (m, 1H, *CH_2*-CH), 3.25 (dd, J=13.9, 3.8 Hz, 1H, 6-CH_2), 3.76 (s, 6H, CO_2CH_3), 4.07 (m, 2H, 3-H and CH_2-*CH*), 4.20 (m, 1H, 6-H), 6.20 (s, 1H, 1-H), 7.12-7.37 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.5 (3-CH_3), 34.3 (CH_2-*CH*), 40.7 (6-CH_2), 48.0 (*CH_2*-CH), 52.7 (OMe), 56.4 and 57.8 (C-6 and C-3), 127.4, 128.8, 129.7 and 135.1 (Ph), 161.6 (C-5), 169.5 and 171.4 (CO).

Synthesis of 1-substituted 7-benzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazines.

A solution of the corresponding 1,7-disubstituted pyrrolopyrazine (0.36 mmol) in THF (8 mL) was treated under Ar atmosphere, with freshly prepared NaOMe (0.03 g, 0.54 mmol). After being stirred for 5 min, benzyl bromide (0.07 mL, 0.65 mmol) was added. The mixture was stirred overnight and then evaporated. The residue was extracted with EtOAc and washed with H_2O and brine, dried (Na_2SO_4) and evaporated to dryness. Compounds were purified on a silica gel column using the solvent system specified in each case.

7-Benzyl-1-methyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines. Chromatographic solvent system: gradient from 1 to 3% of MeOH in CH_2Cl_2. Isomer (1*S*, 7*R*, 8a*R*) **18**. Yield 57%, foam (From **13a**). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85. Found: C 64.82, H 6.22, N 9.13. Isomers (1*S*, 7*RS*, 8a*S*) **20+22**. Yield 56%, foam (**20/22**= 1:3.5, from **13b**). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85. Found: C 64.63, H 6.69, N 8.54.

1,7-Dibenzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines. Chromatographic solvent system: gradient from 2 to 5% of MeOH in CH_2Cl_2. Isomer (1*S*, 7*R*, 8a*R*) **19** Yield 52%, foam (from **14a**). Anal. Calcd for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 70.17, H 6.58, N 6.82. Isomers (1*S*, 7*R*, 8a*S*) and (1*S*, 7*S*, 8a*S*) **21+23** Yield 34%, syrup (from **14b**) Anal. Calcd for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 70.25, H 6.49, N 6.97.

^{1}H NMR data of these compounds are recorder in Table 3.

Table 3. Significant ^{1}H NMR Data of Di- and Trisubstituted Perhydropyrrolo[1,2-*a*]pyrazines (300 MHz, $CDCl_3$).

Compd	δ(ppm)								$J_{1,2}$	$J_{1,8a}$
	H-1	H-2	H-4		H-7	H-8		H-8a	(Hz)	(Hz)
13a	3.63	7.48	3.78	4.44	3.56	2.08	2.67	4.18	1.5	3.6
		7.55	3.79	4.31	6.63	2.33	2.45	4.02	3.4	3.5
13b	3.25	7.19	3.67	4.36	3.49	1.90	2.62	3.49	0	9.5
	3.49	7.09			3.32	2.13	2.46		0	-
14a	3.58	6.32	3.74	4.41	3.58	2.22	2.71	4.26	4.9	4.8
		6.39		4.23		2.50		4.09	4.1	-
14b	3.57	5.96	3.84	4.50	3.71	2.02	2.71	3.71	0	9.6
	3.71	5.92	3.83		3.57	2.35	2.54		0	-
16a	3.65	6.18	4.18		3.54	2.39		4.02	3.7	3.4
	3.65	6.17	4.19		3.57	2.18	2.50	4.33	4.9	3.1
16b	3.47	5.74	4.53		3.60	2.03	2.66	3.79	0	9.8
	3.72	5.70	4.53		3.60	2.32	2.51	3.60	0	10.6
16c (7*R*)	3.93	5.77	4.99		3.37	2.08	2.50	5.02	0	-
16c (7*S*)	4.39	5.79	4.86		3.43	2.31		4.72	0	-
18	3.27	5.97	4.16	3.35	-	2.35	2.27	2.60	-	-
20[a]	2.20	6.50	4.28	3.65	-	2.55	1.60	3.25	-	-
22[a]	3.23	6.50	4.28	3.31	-	2.28	2.20	2.12	-	-
19	3.32	6.00	4.19	3.37	-	2.25		2.70	-	-
21[b]	2.25	5.63	4.31	3.68	-	2.55	1.75	3.40	-	-
23[b]	3.35	5.78	4.30	3.27	-	2.25		2.25	-	-

[a] From the **20+22** mixture. [b] From the **21+23** mixture

ACKNOWLEDGEMENTS

We thank the Comisión Interministerial de Ciencia y Tecnología (SAF 94 0705), Ministerio de Educación y Ciencia (UE 95-0021) and Comunidad de Madrid (AE 00004/95) for financial support.

REFERENCES

1. P. C. Bélander and C. Dufresne, *Can. J. Chem.* 1986, **64,** 1514.
2. a) R. Hirschmann, K. C. Nicolaou, S. Pietranico, E. M. Leahy, J. Salvino, B. Arison, M. A. Cichy, P. G. Spoors, W. C. Shakespeare, P. A. Sprengeler, P. Hamley, A. B. Smith, III, T. Reisine, K. Raynor, L. Maechler, C. Donaldson, W. Vale, R. M. Freidinger, M. R. Cascieri, and C. D. Strader, *J. Am. Chem. Soc.*, 1993, **115**, 12550. b) R. Hirschmann, P. A. Sprengeler, T. Kawasaki, J. W. Leahy, W. C. Shakespeare, and A. B. Smith, III, *J. Am. Chem. Soc.*, 1992, **114**, 9699.
3. D. L. Flynn, C. I. Villamil, D. P. Becker, G. W. Gullickson, C. Moummi, and D. C. Yang, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 1251.
4. G. L. Olson, D. R. Bolin, M. P. Bonner, M. Bös, C. M. Cook, D. C. Fry, B. J. Graves, M. Hatada, D. E. Hill, M. Kahn, V. S. Madison, V. K. Rusiecki, R. Sarabu, J. Sepinwall, G. P.Vincent, and M.E. Voss, *J. Med. Chem.*, 1993, **36**, 3039.
5. a) G. Holzemann, *Kontakte*, 1991, 3 and 55. b) M. Kahn, *Synlett*, 1993, 821. c) R. M. J. Liskamp, *Recl. Trav. Chim. Pays-Bas*, 1994, **113**, 1.
6. R. M. Fredinger, D.F. Veber, D. S. Perlow, J. R. Broods,and R. Saperstein, *Science*, 1980, **210**, 656.
7. a) K. Sato and U. Nagai, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1231. b) M. J. Genin and R. L. Johnson, *J. Am. Chem. Soc.*, 1992, **114**, 8778. c) M. J. Genin, W. B. Gleason, and R. L. Johnson, *J. Org. Chem.*, 1993, **58**, 860. d) H.-G. Lombart and W. D. Lubell, *J. Org. Chem.*, 1994, **59**, 6147. e) D. S. Kemp and Z. Q. Li, *Tetrahedron Lett.*, 1995, **36**, 4175. f) S. Hanessian, B. Ronan, and A. Laoui, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1397. g) J. A. Robl, *Tetrahedron Lett.*, 1994, **35**, 393. h) R. Mueller and L. Revesz, *Tetrahedron Lett.*, 1994, **35**, 4091. i) S. Hanessian and G. McNaughton-Smith, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1567. j) U. Slomczynskaya, D. K. Chalmer, F. Cornille, M. L. Smythe, D. D. Beusen, K. D. Moeller, and G. R. Marshall, *J. Org. Chem.*, 1996, **61**, 1198.
8. P. S. Farmer and E. J. Ariëns, *Trends Pharmacol. Sci.*, 1982, **3**, 362.
9. M. Martín-Martínez,,M. T. García-López, R. Herranz, and R. González-Muñiz, *Tetrahedron*, 1995, **51**, 10361.
10. S. Okada, A. Kosasayama, T. Konno, and F. Uchimaru, *Chem. Pharm. Bull.*, 1971, **19**, 1344.
11. C. Chang, J. D. Cocker, H. G. Davies, A. Gore, and R. H. Green, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 161.
12. M. J. Domínguez, M. T. García-López, R. Herranz, M. Martín-Martínez, and R. González-Muñiz, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2839.
13. A. I. Meyers and R. H. Wallace, *J. Org. Chem.*, 1989, **54**, 2509.

Received, 19th May, 1997